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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,872		Hubertus Johannes Marie Op Den Camp	28902.0008.	1317

30827 7590 04/11/2007
MCKENNA LONG & ALDRIDGE LLP
1900 K STREET, NW
WASHINGTON, DC 20006

EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	**PAPER NUMBER**
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,872	OP DEN CAMP ET AL.	
	Examiner	Art Unit	
	Christian L. Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *SEQUENCE ERROR REPORT*.

DETAILED ACTION

1. Claims 1-20 are pending and under consideration in this Office Action.

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR §§ 1.821 through 1.825 for the reason(s) set forth in the enclosed RAW SEQUENCE LISTING ERROR REPORT dated 02/17/2005.

Appropriate correction is requested. Submission of a new paper copy of the Sequence Listing, a computer readable form of the corrected Sequence Listing, and statement that the computer readable form is identical to the paper Sequence Listing is required.

5. The information disclosure statement filed 07/07/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated eukaryotic host cell transformed with a polynucleotide encoding a xylose isomerase consisting of the amino acid sequence of SEQ ID NO: 1; does not reasonably provide enablement any other embodiment as recited in the claims. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized In re Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claims encompass any eukaryotic host cell transformed with any nucleic acid construct comprising any nucleotide sequence encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO: 1.

The specification provides guidance and working example for an isolated polynucleotide from *Piromyces* sp. E2 (ATCC 76762) encoding a xylose isomerase consisting of the amino acid sequence of SEQ ID NO: 1, yeast expression vectors containing said isolated polynucleotide, yeast host cells transformed with said expression vectors, and growth of said yeast host cells on xylose (see Examples 1-4). However, the specification does not provide guidance, working examples, or prediction for making any polynucleotide encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO: 1. Furthermore, the specification does not provide guidance, working examples, or prediction for making the genetic modifications recited in claims 7-11.

Thus, an undue amount of trial and error experimentation must be preformed where such experimentation involves searching and screening a vast number of biological sources for the claimed polynucleotide encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO: 1. Alternatively, trial and error experimentation must then be performed to search and screen for specific amino acid residues in SEQ ID NO: 1 to change (e.g., amino acid deletion, insertion, substitution, and combinations thereof) which will not result in inactivation of xylose isomerase activity. General teaching regarding screening and searching for the claimed invention is not guidance for making the claimed invention.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific amino acid residues in SEQ ID NO: 1 which does not affect enzyme activity. Without such a guidance, the amount of experimentation left to those skilled in the art to make the invention is undue and well outside of routine experimentation.

Furthermore, the claims are so broad as to encompass host cells transformed with the recite nucleic acid construct, including cells in *in vitro* culture as well as cells within any multicellular organism. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of host cells broadly encompassed by the claims. While methods for transforming cells *in vitro* are well known in the art, methods for successfully transforming cells within complex multicellular organisms are not routine and are highly unpredictable. Furthermore, methods for producing a successfully transformed cell within one multicellular organism are unlikely to be applicable to transformation

of other types of multicellular organisms as multicellular organisms vary widely. However, in this case the disclosure is limited to only host cells *in vitro*. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the use of host cells within a multicellular organism for the production of polypeptide. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, expression of nucleic acids in a particular host cell and having the desired biological characteristics is unpredictable the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

8. Claims 12-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required are summarized In re Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claims encompass any process for producing ethanol, lactic acid, acetic acid, succinic acid, any amino acid, 1,3-propanediol, ethylene, glycerol, any β-lactam, or cephalosporin using any eukaryotic host cell transformed with any nucleic acid construct comprising any nucleotide sequence encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO: 1.

The specification provides guidance and working example for an isolated polynucleotide from *Piromyces* sp. E2 (ATCC 76762) encoding a xylose isomerase consisting of the amino acid sequence of SEQ ID NO: 1, yeast expression vectors containing said isolated polynucleotide, yeast host cells transformed with said expression vectors, and growth of said yeast host cells on xylose (see Examples 1-4). However, the specification does not provide guidance, working examples, or prediction for making any polynucleotide encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO: 1 and any eukaryotic host cell transformed with said polynucleotide that can be used in any process for producing ethanol, lactic acid, acetic acid, succinic acid, any amino acid, 1,3-propanediol, ethylene, glycerol, any β-lactam, or cephalosporin. Furthermore, the specification does not provide guidance, working examples, or prediction for making the recited genetic modifications recited in claims 7-11 and 16.

The state of the art as exemplified by van Maris et al. (Antonie Van Leeuwenhoek. 2006

Nov; 90(4): 391-418. Epub 2006 Oct 11) is of the lack of success of heterologous expression of xylose isomerase in yeast for the production of ethanol due to improper protein folding, posttranslational modifications, disulfide-bridge formation, and the internal pH of yeast (see entire publication, especially pps. 400-401).

Thus, an undue amount of trial and error experimentation must be preformed where such experimentation involves searching and screening a vast number of biological sources for the claimed polynucleotide encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO: 1 and then determining whether transforming the polynucleotide in any host cell will enable that host cell to make ethanol, lactic acid, acetic acid, succinic acid, any amino acid, 1,3-propanediol, ethylene, glycerol, any β-lactam, or cephalosporin. Alternatively, trial and error experimentation must then be performed to search and screen for specific amino acid residues in SEQ ID NO: 1 to change (e.g., amino acid deletion, insertion, substitution, and combinations thereof) which will not result in inactivation of xylose isomerase activity and then determining whether transforming the polynucleotide in any host cell will enable that host cell to make ethanol, lactic acid, acetic acid, succinic acid, any amino acid, 1,3-propanediol, ethylene, glycerol, any β-lactam, or cephalosporin. General teaching regarding screening and searching for the claimed invention is not guidance for making the claimed invention. Thus, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

9. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a genus of eukaryotic host cells transformed with any nucleic acid construct comprising any nucleotide sequence encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO: 1 and genus of processes for producing ethanol, lactic acid, acetic acid, succinic acid, any amino acid, 1,3-propanediol, ethylene, glycerol, any β-lactam, or cephalosporin using said genus of eukaryotic host cells.

The scope of the genus includes many members with widely differing structural, chemical, and physiochemical properties including widely differing amino acid/nucleotide sequences and biological functions for the protein/enzymes in the recited biosynthetic pathways. Furthermore, each genus is highly variable because a significant number of structural and biological differences between genus members exist.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by

functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant application, the specification discloses only an isolated polynucleotide from *Piromyces* sp. E2 (ATCC 76762) encoding a xylose isomerase consisting of the amino acid sequence of SEQ ID NO: 1, yeast expression vectors containing said isolated polynucleotide, yeast host cells transformed with said expression vectors, and growth of said yeast host cells on xylose (see Examples 1-4).

The specification fails to disclose additional eukaryotic host cells as encompassed by the claimed, which are widely variant in their physiological characteristics, functions, and/or structures. The specification does not describe production of ethanol, lactic acid, acetic acid, succinic acid, any amino acid, 1,3-propanediol, ethylene, glycerol, any β-lactam, or cephalosporin using said the above mentioned yeast host cells transformed with said expression vectors. Furthermore, the specification does not provide a written description of the genetic modifications recited in claims 7-11 and 16.

The disclosure of the above mentioned yeast host cells transformed with said expression vectors is insufficient to be representative of the attributes and features common to all the members of the claimed genus. Thus, one skilled in the art cannot visualize or recognize the identity of the members of each genus.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definitions, such as the structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v, Eli Lilly and Co.* 43 USPQ2d 1398 (Fed. Cir. 1997), quoting *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe the genus of genetic materials, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g. structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these. Therefore, the instant claims are not adequately described.

In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of a genus of eukaryotic host cells transformed with any nucleic acid construct comprising any nucleotide sequence encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO: 1 and genus of processes for

producing ethanol, lactic acid, acetic acid, succinic acid, any amino acid, 1,3-propanediol, ethylene, glycerol, any β-lactam, or cephalosporin using said genus of eukaryotic host cell.

Claim Rejections - 35 U.S.C. § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guan et al. (US Patent 5,643,758; published 07/01/1997) or Karlsson et al. (Eur J Biochem. 2001 Dec;268(24):6498-507) in view of Accession Q9P8C9 (published 2000-10-01).

Guan et al. teach expression vectors containing promoters, prokaryotic host cells such as *E. coli* and eukaryotic host cells such as yeast, and methods for making, expressing, isolating, and purifying any protein fused to the *E.coli* maltose binding protein (MBP) using the said expression vectors, prokaryotic and eukaryotic host cells such as yeast; and that these methods and products are useful for purifying virtually any hybrid polypeptide molecule employing recombinant techniques (see entire patent).

Karlsson et al. teach the filamentous fungus *Trichoderma reesei* host cell transformed with an expression vector containing a polynucleotide encoding Ce161A (EG IV) (see entire publication).

The teachings of Guan et al. and Karlsson et al. differs from the claims in that the yeast host cell or the filamentous fungus *Trichoderma reesei* host cell not transformed with a polynucleotide encoding a xylose isomerase comprising an amino acid sequence that has at least 70% identity to SEQ ID NO; 1.

Accession Q9P8C9 teach a xylose isomerase having an amino acid sequence that is 100% identical to SEQ ID NO: 1 (see attached alignment).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use transform the yeast host cell taught by Guan et al. or *Trichoderma reesei* host cell taught by Karlsson et al. with the polynucleotide encoding the xylose isomerase taught by Accession Q9P8C9 having an amino acid sequence that is 100% identical to SEQ ID NO: 1. One

of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to express and purify the xylose isomerase taught by Accession Q9P8C9. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for success because recombinant molecular biology techniques for heterologous or homologous expression of proteins is well developed in the art.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

14. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF

TEKCHAND SAIDHA
PRIMARY EXAMINER

STIC Biotechnology Systems Branch

RAW SEQUENCE LISTING ERROR REPORT

The Biotechnology Systems Branch of the Scientific and Technical Information Center (STIC) detected errors when processing the following computer readable form:

Application Serial Number: 10/500,872
Source: PCT
Date Processed by STIC: 2-17-05

THE ATTACHED PRINTOUT EXPLAINS DETECTED ERRORS.
PLEASE FORWARD THIS INFORMATION TO THE APPLICANT BY EITHER:

1) **INCLUDING A COPY OF THIS PRINTOUT IN YOUR NEXT COMMUNICATION TO THE APPLICANT, WITH A NOTICE TO COMPLY or,**
2) **TELEPHONING APPLICANT AND FAXING A COPY OF THIS PRINTOUT, WITH A NOTICE TO COMPLY**

FOR CRF SUBMISSION AND PATENTIN SOFTWARE QUESTIONS, PLEASE CONTACT MARK SPENCER, TELEPHONE: 571-272-2510; FAX: 571-273-0221

TO REDUCE ERRORED SEQUENCE LISTINGS, **PLEASE** USE THE **CHECKER VERSION 4.2.2 PROGRAM**, ACCESSIBLE THROUGH THE U.S. PATENT AND TRADEMARK OFFICE WEBSITE. SEE BELOW FOR ADDRESS:

http://www.uspto.gov/web/offices/pac/checker/chkrnote.htm

Applicants submitting genetic sequence information electronically on diskette or CD-Rom should be aware that there is a possibility that the disk/CD-Rom may have been affected by treatment given to all incoming mail.
Please consider using alternate methods of submission for the disk/CD-Rom or replacement disk/CD-Rom.
Any reply including a sequence listing in electronic form should NOT be sent to the 20231 zip code address for the United States Patent and Trademark Office, and instead should be sent via the following to the indicated addresses:

1. EFS-Bio (<http://www.uspto.gov/ebc/efs/downloads/documents.htm> , **EFS Submission User Manual** - ePAVE)
2. **U.S. Postal Service:** Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
3. **Hand Carry, Federal Express, United Parcel Service, or other delivery service (EFFECTIVE 01/14/05):** U.S. Patent and Trademark Office, Mail Stop Sequence, Customer Window, Randolph Building, 401 Dulany Street, Alexandria, VA 22314

Revised 01/24/05

PCT

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HARHANGI, Harry Ramanoedj
VAN DER DRIFT, Christiaan
PRONK, Jacobus Thomas
<120> TITLE OF INVENTION: Fermentation of pentose sugars
<130> FILE REFERENCE: 28902.0008
<140> CURRENT APPLICATION NUMBER: 10/500,872
<141> CURRENT FILING DATE: 2004-07-07
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Does Not Comply
Corrected Diskette Needed
(pg. 2-4)

ERRORED SEQUENCES

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Invalid Amino Acid

RAW SEQUENCE LISTING DATE: 02/17/2005
PATENT APPLICATION: US/10/500,872 TIME: 12:20:46

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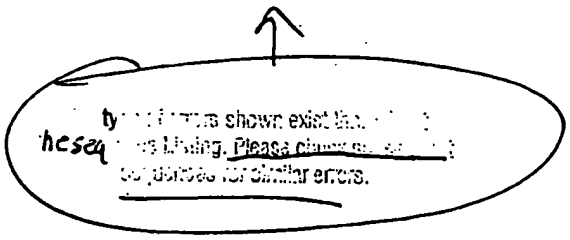
     216 Pro Glu Ala Phe Ala Asn Leu Lys Tyr Ile Met Leu Pro His Asp Tyr
     217 145 What is this?   150                 155                 160
     219 Leu Asn Trp Lys Leu Thr Gly Asp Tyr Val Met Glu Tyr Gly Asp Ala
     220                 165                 170                 175
E--> 222 Ser Gly Thr Asn Leu Phe Asp Ser Lys Asn Arg Cys Trp Ser Lys Lys
E--> 223             180                 185                 190
     225 Ile Cys Asp Ile Ile Asp Pro Lys Leu Leu Asp Leu Leu Pro Lys Leu
E--> 226         195                 200                 205
     228 Ile Glu Pro Ser Ala Pro Ala Gly Lys Val Asn Asp Glu Ala Ala Lys
E--> 229     210                 215                 220
     231 Ala Tyr Gly Ile Pro Ala Gly Ile Pro Val Ser Ala Gly Gly Gly Asp
E--> 232 225                 230                 235                 240
     234 Asn Met Met Gly Ala Val Gly Thr Gly Thr Val Ala Asp Gly Phe Leu
E--> 235                 245                 250                 255
     237 Thr Met Ser Met Gly Thr Ser Gly Thr Leu Tyr Gly Tyr Ser Asp Lys
E--> 238             260                 265                 270
     240 Pro Ile Ser Asp Pro Ala Asn Gly Leu Ser Gly Phe Cys Ser Ser Thr
E--> 241         275                 280                 285
     243 Gly Gly Trp Leu Pro Leu Leu Cys Thr Met Asn Cys Thr Val Ala Thr
E--> 244     290                 295                 300
     246 Glu Phe Val Arg Asn Leu Phe Gln Met Asp Ile Lys Glu Leu Asn Val
E--> 247 305                 310                 315                 320
     249 Glu Ala Ala Lys Ser Pro Cys Gly Ser Glu Gly Val Leu Val Ile Pro
E--> 250                 325                 330                 335
E--> 252 Phe Phe Asn Gly Glu Arg Thr Pro Asn Leu Pro Asn Gly Arg Ala Ser
E--> 253             340                 345                 350
     255 Ile Thr Gly Leu Thr Ser Ala Asn Thr Ser Arg Ala Asn Ile Ala Arg
E--> 256         355                 360                 365
     258 Ala Ser Phe Glu Ser Ala Val Phe Ala Met Arg Gly Gly Leu Asp Ala
E--> 259     370                 375                 380
     261 Phe Arg Lys Leu Gly Phe Gln Pro Lys Glu Ile Arg Leu Ile Gly Gly
E--> 262 385                 390                 395                 400
     264 Gly Ser Lys Ser Asp Leu Trp Arg Gln Ile Ala Ala Asp Ile Met Asn
E--> 265                 405                 410                 415
     267 Leu Pro Ile Arg Val Pro Leu Leu Glu Glu Ala Ala Ala Leu Gly Gly
E--> 268             420                 425                 430
     270 Ala Val Gln Ala Leu Trp Cys Leu Lys Asn Gln Ser Gly Lys Cys Asp
E--> 271         435                 440                 445
     273 Ile Val Glu Leu Cys Lys Glu His Ile Lys Ile Asp Glu Ser Lys Asn
```

ASN

RAW SEQUENCE LISTING DATE: 02/17/2005
PATENT APPLICATION: US/10/500,872 TIME: 12:20:46

Input Set : A:\NOB-8 Seq List (28902.0008).txt
Output Set: N:\CRF4\02172005\J500872.raw

```
E--> 274     450                 455                 460
     276 Ala Asn Pro Ile Ala Glu Asn Val Ala Val Tyr Asp LYS Ala Tyr Asp
E--> 277 465                 470                 475                 480
     279 Glu Tyr Cys Lys Val Val Asn Thr Leu Ser Pro Leu Tyr Ala
E--> 280                 485                 490
```



VERIFICATION SUMMARY DATE: 02/17/2005
PATENT APPLICATION: US/10/500,872 TIME: 12:20:47

Input Set : A:\NOB-8 Seq List (28902.0008).txt
Output Set: N:\CRF4\02172005\J500872.raw

L:66 M:330 E: (2) Invalid Amino Acid Designator, NUMBER OF INVALID KEYS:1
L:222 M:333 E: Wrong sequence grouping, Amino acids not in groups!
L:222 M:330 E: (2) Invalid Amino Acid Designator, NUMBER OF INVALID KEYS:2
L:223 M:332 E: (32) Invalid/Missing Amino Acid Numbering, SEQ ID:3
M:332 Repeated in SeqNo=3
L:252 M:333 E: Wrong sequence grouping, Amino acids not in groups!
L:252 M:330 E: (2) Invalid Amino Acid Designator, NUMBER OF INVALID KEYS:3
L:280 M:252 E: No. of Seq. differs, <211> LENGTH:Input:494 Found:497 SEQ:3